REMARKS

I. Indefiniteness Rejection under §112, Second Paragraph:

A. Claims 100-105, 107, 108, 111-123, 127, 129-143

Claims 100-105, 107, 108, 111-123, 127, 129-135 are being rejected as being incomplete and omitting essential elements. The Office Action states that "the omitted elements involve the relation of the method of regulating expression to the transgenic animal and further the relation between the first and second nucleic acid cassettes." In particular, the Office Action states that "it is unclear how the claimed method recited in the preamble relates to either of the element (a) or (b)." Applicants have amended claim 100 and respectfully submit that the amendment overcomes the rejection. Amended claim 100 now recites:

100. (Twice Amended) A method of regulating expression of a desired protein or RNA in an animal, said method comprising:

administering to said animal a pharmacological dose of a ligand which binds to a mutated steroid receptor superfamily ligand binding domain,

wherein said animal contains:

(a) a first nucleic acid cassette which comprises a promoter transcriptionally linked to a mutated receptor protein coding sequence,

wherein said mutated receptor protein coding sequence comprises a nucleic acid sequence encoding a mutated receptor protein which regulates the transcription from a molecular switch promoter, and wherein said mutated receptor protein comprises:

a DNA binding domain which binds said molecular switch promoter;

the mutated steroid hormone receptor superfamily ligand binding domain, which is distinct from a naturally occurring ligand binding domain;

a transactivation domain which causes transcription from said molecular switch promoter when said mutated receptor protein is bound to said molecular switch promoter and to the ligand which is an antagonist for a nonmutated receptor protein; and

(b) a second nucleic acid cassette comprising a nucleic acid encoding the desired protein or RNA transcriptionally linked to said molecular switch promoter[, a nucleic acid encoding a desired protein in a second nucleic acid cassette]; wherein administration of said ligand regulates expression of said desired protein or RNA in said animal.

The preamble is amended to regulating expression of a desired protein or RNA. As amended, the desired protein or RNA is encoded by nucleic acid contained in the second nucleic acid cassette (element b). The nucleic acid encoding the desired protein or RNA is transcriptionally linked to the molecular switch promoter, which is regulated by the mutated receptor protein encoded by the mutated receptor protein coding sequence of element (a). Thus, the preamble relates to elements (a) and (b).

The Office Action also states that "it is unclear whether the nucleic acid cassettes are or are not regulated by the ligand administered to the animal." Applicants respectfully submit that the claim clearly recites that "administration of said ligand regulates expression of said desired [protein or RNA] in said animal," which is encoded by the nucleic acid comprised in the second nucleic acid cassette. The claim is also amended to recite that the mutated receptor protein comprising the "transactivation domain causes transcription from said molecular switch promoter when said mutated receptor protein is bound to said molecular switch promoter and to the ligand." The confusion over the initial claim may have been due to the reintroducing in element (a) of "a mutated steroid hormone receptor superfamily ligand binding domain" that has already been introduced earlier in the claim. Thus, Applicants have amended the claim to recite "the mutated steroid

hormone receptor superfamily ligand binding domain, which is distinct from a naturally occurring ligand binding domain."

The Office Action further states that "it is ... unclear in part (a) what might be the purpose of transcribing a promoter.... [since p]romoters are generally not transcribed in eukaryotic cells, but rather drive the transcription of an associated gene." Applicants have amended the element (a) to recite "transcription from a molecular switch promoter," instead of the original language "transcription of a molecular switch promoter," which was objectionable. Thus, Applicants respectfully ask that the rejection be withdrawn.

B. Claims 135-143

Claims 135-143 are being rejected as being incomplete and omitting essential elements. The Office Action states that "as the claim is written, essential elements are missing involving the bridge "activation" and "regulation." In particular, the Office Action states that "it is unclear how the two elements are related. For example, it is not apparent that regulated expression is or is not dependent upon "activation" of the molecular switch." Applicants have amended claim 135 to recite the following and amended claim should now overcome the rejection:

> 135. (Amended) A method of regulating expression from a desired protein or RNA in an animal comprising:
>
> administering to the animal a pharmacologic dose of a ligand that activates a molecular switch protein encoded by a first expression cassette comprised in the animal, wherein the activation of the molecular switch protein results in expression of the desired protein or RNA from a second expression cassette comprised in the animal, wherein the molecular switch comprises a mutated steroid hormone superfamily receptor ligand binding domain which is activated by the

administered ligand but not by a native ligand for a corresponding wild type steroid hormone superfamily receptor ligand binding domain.

The Office Action also states that "claim 135 is further unclear because the use of the term 'capable' ... does not distinctly set forth the metes and bounds of the claimed subject matter." The claim has been amended to delete the objectionable term. Thus, Applicants respectfully ask that the rejection be withdrawn.

C. Claims 100-105, 107, 108, 111-123, 127, 129-143

Claims 100-105, 107, 108, 111-123, 127, 129-143 are also rejected as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office Action states that "it is not clear that the use of the term, [molecular switch,] is consistent between claims 100 and 135, ... [because] it is ambiguous as to whether molecular switch refers to a nucleic acid sequence or a protein." Applicants have amended claim 135 to recite a "molecular switch protein" to clearly delineate it from the "molecular switch promoter" (nucleic acid) of claim 100. Thus, Applicants respectfully ask that the rejection be withdrawn.

II. Written Description Rejection Under §112, First paragraph.

A. The genus of "desired gene" or "desired protein"

Claims 100-105, 107, 108, 111-123, 129-143 are being rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Office Action states that "the instant application lacks written description for claimed subject matter encompassed by the term 'desired gene,' or alternatively, 'desired protein," [because] the specification fails to describe the genus of 'desired genes' or 'desired proteins' encompassed in the claims with particularity to indicate

that Applicants had possession of the claimed invention. Applicants respectfully traverse this rejection.

The "desired protein or RNA" can be any protein or RNA for which regulation of the expression is desired. A person of ordinary skill in the art of molecular biology can readily splice various nucleic acids encoding proteins or RNAs into the expression vector that Applicants have disclosed. For example, the protein can be a growth factor (Spec., p. 18, l. 7), chloroamphenicol acyltransferase (CAT) (Spec., Example 15, p. 31), or lactoferrin (Spec., p. 34). At the time of the filing of this application, CAT was routinely used by people ordinarily skilled in the art as a reporter for expression. Expression of CAT was deemed to be representative and reasonably correlated to expression of any protein. See e.g. U.S. Patent No. 5,082,779.[1] Thus, the specification has sufficiently and particularly disclosed species that a person of ordinary skill in the art would reasonably deem to be representative within the genus.

The Office Action also states that the "claimed embodiments of any and all desired genes, desired proteins and resultant phenotypes lack written description[, because] the skilled artisan cannot envision the detailed structure and phenotypic effect of the nucleic acid constructs, genes, and/or proteins of all of the encompassed claimed embodiments and therefore conception is not achieved until reduction to practice has occurred." (original emphasis). Applicants respectfully traverse.

With respect to the Office Action requiring reduction to practice of all genes, Applicants respectfully submit that this is not the standard for written description. "The written description

[1] A copy is provided for the convenience of the Examiner, as attachment A. The 5,082,779 patent, issued January 21, 1992, used CAT as a reporter gene, but broadly claimed "expressing a non-prolactin gene" by "operably linking said gene to a developmentally specific prolactin promoter" in a transgenic animal. *See* Claim 1.

requirement for a claimed genus may be satisfied through sufficient description of a representative number of species." MPEP 2163, (II)(3)(a)(i). "There may be situations where one species adequately supports a genus," especially when the claimed genus is auxiliary to the invention. *Id* citing *In re Herschler*, 591 F.2d 693, 697 (CCPA 1979) (disclosure of corticosteroid in DMSO sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO because "the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description.") (emphasis added).

Applicants have created a regulatable expression system and taught its use *in vivo* in an animal. The claimed language to "desired gene" or "desired protein" is auxiliary to the invention of the vector system and its applications to use *in vivo*. A person of ordinary skill in the art would understand that such a regulatable expression system can be applied to express any RNA or protein and the use of CAT as a reporter is an accepted way of reducing the invention to practice. See e.g. U.S. Patent No. 5,082,779. To require that Applicants disclosed the specific sequence of "any and all" genes that are within the genus of "desired gene" or "desired protein" is to require, for example, that a new method for sequencing a gene disclosed all genes, which it can be used for. But many patents have been issued on expression vectors or sequencing methods that can be applied to any "desired gene" where the disclosure did not provide all genes.

With respect to the Office Action requiring disclosure of "phenotypic effect," Applicants respectfully submit that "phenotypic effect" is not a limitation of the claims. To the extent that "expression of a desired gene" connotes "phenotypic effects," Applicants have amended the claims

to recite expression of protein or RNA. Therefore, Applicants respectfully requests withdrawal of the rejection.

B. "mutated steroid hormone superfamily receptor ligand bind domain"

The Office Action states that "claims 100-105, 107, 108, 111-123, 127, 129-143, are broadly drawn to encompass any and all mutations to steroid receptors such that said mutated receptors are capable of binding ligands which are not "naturally occurring." It further states that "the applicants have clearly not delineated a representative number of mutations of the genus of receptor mutations involving the ability to bind any and all non-naturally occurring ligands such that possession of the claimed invention would be apparent to one of skill in the art." Hence, the Office Action concludes that "the disclosure lacks written description for the genus of mutated steroid hormone receptor."

Applicants respectfully traverse. Applicants have provided deletion mutants that are representative of the mutated ligand binding domain and has taught the methods for obtaining and verifying the activity of the mutants. Based on Applicants' teaching, a person of ordinary skill in the art would be able to use known mutagenesis protocols and based on Applicants' teaching arrive at other mutants of the steroid hormone receptor ligand binding domain, the non-mutated sequence of which was already known at the time of filing of this application. Thus, Applicants respectfully ask the withdrawal of this rejection.

III. Enablement Rejection Under §112, First paragraph

A. "Phenotypic Effects"

Claims 100-105, 107, 108, 111-123, 127, 129-143 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are rejected because the Office Action first states that "the gene driven by the modified receptor is not recited in the claims and hence could be any gene known to man or indeed any nucleic acid without a known function." The Office Action is correct in that the gene or nucleic acid can be any gene or nucleic acid. But as discussed above, the gene or protein is auxiliary to the invention and a person of ordinary skill in the art would understand and know how to splice in various genes into the expression vector that Applicants have taught. If the gene function is unknown, then Applicants' invention is useful in helping to elucidate the function by allowing controlled expression of the gene, just as a method of sequencing a gene helps to elucidate the sequence of unknown genes.

The Office Action also states that "Applicants do not provide any means for discerning what sort of phenotype might be involved in any gene regulated by the mutated receptor.... For the invention to function as claimed, at least two genes must be introduced into an animal. The first being the mutated receptor and the second being the receptor driven reporter gene.... Applicants have prospectively suggested one mutated receptor which might function, but have neither disclosed nor recited any particular phenotype caused by transformation of an animal and have not demonstrated an animal which has a phenotype which may be modulated by a molecular switch protein."

The Office Action further states that "while the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic mammals comprising a transgene of interest; it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype." Applicants respectfully traverse.

In response to this rationale, Applicants respectfully submit that the claims, as amended, recite expression of protein or RNA, and do not have a limitation requiring phenotypic effect. This

case is analogous to *Ex Parte Chen* where the Board of Patent Appeals and Interference reversed the examiner's rejection on lack of enablement of a claim to transgenic carp because the examiner was requiring enablement of limitations not present in the claims:

> The examiner's concerns relating to reproducibility of the exact carp, phenotypic characteristics, levels of expression, and reproducibility of identical fish are misplaced, because the claims do not include or require these limitations.

61 USPQ2d 1025, 1028 (BPAI 2001) (unpublished).[2] Thus, the rationale for the rejection and the Office Action's discussion of unpredictability of transgenic animal is inapplicable.

B. Evidence of Functioning In Vivo

The Office Action further states that "applicants have not even provided evidence of a marker gene such as luciferase functioning in a transgenic animal in a manner consistent with the claimed scope of the invention." On an initial note, Applicants respectfully submit that the specification disclosed the use of chloroamphenicol acyltransferase (CAT) in Example 15, which is an equivalent reporter gene. A person of ordinary skill in the art would reasonably correlate CAT use *in vitro* to its use *in vivo*.

It is important to delineate the issue addressed by the rejection. The issue is not the methods of generating transgenic animals or methods of delivery of the expression vector in the animal. The Office Action recognized that methods of making transgenic animals are well known in the art. Nor is the issue how to regulate expression because Applicants have disclosed the regulatable expression system can be used in animals. The issue here deals with whether a person of ordinary skill in the art, based on Applicant's disclosure and submitted evidence, would deem the claimed invention "useful" to achieve regulation of expression in an animal. *Cf In re Brana*, 34 USPQ2d 1436 (Fed.

[2] A copy of *Ex Parte Chen* is provided for the convenience of the Examiner, as attachment B.

Cir. 1995) (delineating the issue of asserted specific use of a compound and the issue of whether one skilled in the art would have reasonably questioned the asserted usefulness based on the disclosure and the submitted evidence.)

Applicants respectfully submit that the specification clearly states in Example 17 that the "molecular switch can be used in the production of transgenic animals.... [And o]ne skilled in the art will readily recognize that this protocol can be used for a variety of genes and, thus, it is useful in the regulation of temporal expression of any given gene product in transgenic animals." Spec., p. 33-34. Applicants' specification is presumed to be correct unless the Office Action can point or "explain why it doubts the truth or accuracy of any statement in a supporting disclosure." MPEP § 2164.04.

Furthermore, the specification states that "in another embodiment, the molecular switch/nucleic acid cassette is directly injected into a targeted cell in vivo for gene therapy." p. 18, ll. 3-4. Applicants respectfully submit in this application a copy of the Declaration of Jeff Nordstrom to show that regulation of expression of secreted alkaline phosphatase (SEAP), another reporter protein, in animals using the claimed invention.[3] The data provided in the declaration of Jeff Nordstrom demonstrated that this approach is useful and successful as originally disclosed by the specification. Nordstrom Decl. ¶¶ 4-7. The animals contained the nucleic acid cassettes and the desired gene through intramuscular injection, instillation to the lung, and delivery to the skin. Nordstrom Decl. ¶ 3. The expression of the desired gene was also regulated through the administration of the ligand RU486 (Mifepristone).

[3] The Declaration of Jeff Nordstrom and accompanying exhibits were submitted in a related application, U.S. Patent Application No. 08/454,418 (now U.S. Patent No. 5,935,934), the written description of which is the same as the grandparent application of the present application, U.S. Application Serial No. 08/479,846 (now U.S. Patent 5,874,534).

The additional data provided by the Declaration of Jeff Nordstrom, although filed after the filing date of the application, goes to prove that the specification's disclosure of usefulness in *in vivo* expression was in fact enabling when filed (i.e., demonstrated utility). This type of declaration was explicitly allowed by the Federal Circuit in *In re Brana*, 34 USPQ2d at 1441, n. 19 (declaration filed after filing of application "can be used to substantiate any doubts as to the asserted utility ... and goes to prove that the disclosure was in fact enabling when filed.") Thus, Applicants respectfully ask that the rejection be withdrawn.

C. "mutated steroid hormone receptor superfamily ligand binding domain"

Finally, with respect to the "mutated steroid hormone receptor superfamily ligand binding domain" that binds to the ligand, the Office Action rejected the claims as not being enabled because it states that "given a known ligand, the design of an appropriately folded binding pocket consisting of the correct amino acids requires more than good ideas, but rather trial and error experimentation to generate a construct of the desired activity." Applicants respectfully traverse.

Applicants note that the determination of enablement entails the consideration of various factors.

a) the breadth of the claims
b) the nature of the invention
c) the state of the prior art
d) the level of one of ordinary skill
e) the level of predictability in the art
f) the amount of direction provided by the inventor,
g) the existence of working examples; and
h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis surface B antigens did not satisfy the enablement requirement.)

Applicants respectfully submit that the breadth of the claims does not include all mutations of the steroid hormone receptor superfamily ligand binding domain, but only those that are capable of binding to a ligand that is an antagonist for the non-mutated receptor protein. Applicants also submit that the nature of the invention is the regulation of expression in an animal, but there is no limitation in the claims requiring any particular phenotypic effects. Applicants have provided guidance and teaching as to the construction of the mutated steroid hormone receptor superfamily ligand binding domain and their screening by using the disclosed yeast system and transfection *in vitro* into mammalian cells. Mutagenesis methods including site directed mutagenesis protocols are well known to one of ordinary skill in the art at the time of filing of this application. A person of skill in the art can perform routine screening of mutants generated by the mutagenesis protocol using the screening method taught by the Applicants. Furthermore, Applicants have shown a working example of a mutated steroid hormone receptor superfamily ligand binding domain that was used in the in vitro expression disclosed in the specification and in vivo expression disclosed in the Declaration of Jeff Nordstrom. The Office Action has not addressed why the screening methods taught by Applicants cannot be used as "routine screening" for other mutants. "Enablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 8 USPQ2d at 1404. Thus, Applicants respectfully ask that the enablement rejection be withdrawn.

CONCLUSION

Based on the foregoing arguments and the attached evidence, Applicants respectfully submit that all claims are now allowable. Applicants respectfully ask for a issuance of a notice of allowance.

Respectfully submitted,

LYON & LYON LLP

Dated: 2-28-2002 By: Samuel N. Tiu

Samuel N. Tiu
Reg. 47,997

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PATENT TRADEMARK OFFICE

LYON & LYON LLP / VALENTIS, INC.
633 W. Fifth Street, Suite 4700
Los Angeles, CA 90071
Ph: (213) 489-1600
Fax (213) 955-0440

VERSION OF AMENDMENT SHOWING CHANGES

Please amend the claims as follows:

100. (Twice Amended) A method of regulating expression of a desired [gene] protein or RNA in an animal, said method comprising:

administering to said animal a pharmacological dose of a ligand which binds to a mutated steroid receptor superfamily ligand binding domain,

wherein said animal contains:

(a) a first nucleic acid cassette which comprises a promoter transcriptionally linked to a mutated receptor protein coding sequence,

wherein said mutated receptor protein coding sequence comprises a nucleic acid sequence encoding a mutated receptor protein which regulates the transcription from [of] a molecular switch promoter, and wherein said mutated receptor protein comprises:

a DNA binding domain which binds said molecular switch promoter;

the [a] mutated steroid hormone receptor superfamily ligand binding domain, which is distinct from a naturally occurring ligand binding domain;

a transactivation domain which causes transcription from said molecular switch promoter when said mutated receptor protein is bound to said molecular switch promoter and to the ligand which is an antagonist for a nonmutated receptor protein; and

(b) a second nucleic acid cassette comprising a nucleic acid encoding the desired protein or RNA transcriptionally linked to said molecular switch promoter[, a nucleic acid encoding a

desired protein in a second nucleic acid cassette]; wherein administration of said ligand regulates expression of said desired [gene] protein or RNA in said animal.

113. (Amended) The method of claim 100, wherein the mutated steroid hormone receptor ligand binding domain binds a compound selected from the group consisting of 5 [alpha]α-pregnane-3,2-dione; 11[beta]β-(4-dimethylaminophenyl)-17[beta]β-hydroxy-17[alpha]α-propinyl-4,9-estradiene-3-one; 11[beta]β-(4-dimethylaminophenyl)-17[alpha]α-hydroxy-17[beta]β-(3-hydroxypropyl)-13[alpha]α-methyl-4,9-gonadiene-3-one; 11[beta]β-(4-acetylphenyl)-17 [beta]β-hydroxy-17[alpha.]α--(1-propinyl)-4,9-estradiene-3-one; 11[beta]β-(4-dimethylaminophenyl)-17[beta]β-hydroxy-17-[alpha]α--(3-hydroxy-1 (Z)-propenyl-estra-4,9-diene-3-one; (7[beta]β,11[beta]β,17[beta]β)-11-(4-dimethylaminophenyl)-7-methyl-4',5'-dihydrospiro[[](ester-4,9-diene-17,2'(3'H)-furan)[]]-3-one; (11[beta]β,14[beta]β,17[alpha.]α)-4',5'-dihydro-11-(4-dimethylaminophenyl)- [[](spiroestra-4,9-diene-17,2'(3'H)-furan)[]]-3-one.

135. (Amended) A method of regulating expression from a desired [gene] protein or RNA in an animal comprising:

administering to [an] the animal a pharmacologic dose of a ligand that activates a molecular switch protein encoded by a first expression cassette comprised in the animal, wherein the activation of the molecular switch protein [and] results in [regulated] expression of [a] the desired [gene] protein or RNA from a second expression cassette comprised in the animal, wherein the molecular switch protein comprises a mutated steroid hormone superfamily receptor ligand binding domain which is activated [capable of activation] by the administered ligand but not by a native ligand for a corresponding wild type steroid hormone superfamily receptor ligand binding domain.